REMARKS

Claims 1 and 7 have been amended, and new claim 23 has been added. Claim 19 has been cancelled without prejudice or disclaimer. Claims 1, 3, 7, 17, and 22-24 are pending in the instant application. No new matter has been added as a result of the above-described amendments. The objections and rejections set forth in the Office Action mailed May 18, 2006 have been overcome by amendment.

1. Rejection of claims 1, 3, 17, and 19 under 35 U.S.C. § 102(a)

The Office Action mailed May 18, 2006 asserts a rejection of claims 1, 3, 17, and 19 under 35 U.S.C. § 102(a), as being anticipated by Nuovo, 1998, *Diagnostic Molecular Pathology* 7:158-63. The Action states that Nuovo discloses a reagent comprising a consensus probe cocktail containing "multiple high HPV types" that detectably hybridizes to HPV types 16, 18, 31, 33, 35, and 51, as well as to HPV types 39, 45, 52, 56, 58, 59, 68, and 70, but not to any of the low risk types tested. The Action also states that because the reagent disclosed by Nuovo contains "multiple high HPV types" and at least some of these fragments hybridize to each of the genomic types listed in the instant claims, the reagent disclosed by Nuovo inherently comprises "a plurality of nucleic acid fragments having different nucleotide sequences." The Action states that the reagent disclosed by Nuovo also anticipates claims 17 and 19 since the reagent would have been provided in a container, and further, that the reagent would have been used in a reaction vessel, which is a container.

To support a rejection under 35 U.S.C. § 102, "the four corners of a single, prior art document [must] describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994). The exclusion of even a single claimed element from a reference, no matter how insubstantial or obvious, is enough to negate anticipation. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. (BNA) 193, 198 (Fed. Cir. 1983). The identical invention must also be shown in the single prior art reference in as complete detail as contained in the application against which the reference is cited. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Moreover, the disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue

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experimentation. M.P.E.P § 2121.01; *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 88 (D. Mass 2001) (citing *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986)). A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. M.P.E.P § 2121.01. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531 (Fed. Cir. 1985).

Applicants have amended claim 1 to recite a reagent comprising a plurality of genomic HPV DNA probe sets that comprise a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequences of HPV types 16, 18, 31, 33, 35, and 51, wherein the proportion of total HPV DNA in the reagent that comprises nucleic acid fragments of the first genomic HPV DNA probe set and the proportion of total HPV DNA in the reagent that comprises nucleic acid fragments of the third genomic HPV DNA probe set are decreased relative to the proportions of the total HPV DNA in the reagent that comprise nucleic acid fragments of the other HPV DNA probe sets, and wherein the nucleic acid fragments of the genomic HPV DNA probe sets do not detectably hybridize to the genomic sequence of a low-risk HPV type. Applicants contend that the accompanying Declaration Pursuant to 37 C.F.R. § 1.132 of Gerard J. Nuovo (submitted herewith as Exhibit A) sets forth affirmative evidence establishing that the Nuovo reference neither describes every element of the claimed reagent such that a person of ordinary skill in the art could practice the claimed invention without undue experimentation nor provides an enabling disclosure of the claimed invention.

In particular, while the Nuovo reference discloses the use of Oncor's high-risk HPV consensus probe to detect the oncogenic HPV types 16, 18, 30, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 70, but not the low-risk HPV types 6, 11, 42, 43, and 44, in cervical biopsies by *in situ* hybridization under low stringency conditions (Declaration, para. 3), this reference fails to disclose the specific composition of the Oncor high-risk HPV consensus probe – *i.e.*, this reference discloses neither the particular HPV types comprising the consensus probe nor the proportions of the particular HPV types comprising the consensus probe (*id.* at para. 4). Thus, using the Nuovo

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reference's teachings, as well as knowledge in the art at the time this reference was published, a person of ordinary skill in the art would not be able to determine the particular HPV types or proportions of the particular HPV types comprising the Oncor high-risk HPV consensus probe without undue experimentation. Clearly, if the Nuovo reference discloses neither the particular HPV types comprising the consensus probe nor the proportions of the particular HPV types comprising the consensus probe, it necessarily follows that the Nuovo reference also fails to disclose that the proportions of total HPV DNA in the reagent comprising nucleic acid fragments of HPV type 16 and 31 DNA are decreased relative to the proportions of the total HPV DNA in the reagent comprising HPV type 18, 33, 35, and 51. Applicants contend that because the Nuovo reference does not describe each and every element of the claimed invention such that a person of ordinary skill in the art could practice the claimed invention without undue experimentation or provide an enabling disclosure of the claimed invention, the Nuovo reference cannot anticipate claims 1, 3, and 17 (claims 3 and 17 depend from claim 1). Withdrawal of this rejection is therefore respectfully solicited.

2. Rejections of claims 1, 3, 7, 17, 19, and 22 under 35 U.S.C. § 103(a)

a. Rejection of claims 1, 3, 17, and 19 as being unpatentable over Nuovo *et al.* in view of Cox *et al.*

The Office Action mailed May 18, 2006 maintains a rejection of claims 1, 3, 17, and 19 under 35 U.S.C. § 103(a), as being unpatentable over Nuovo *et al.*, 1995, *J. Histotechnology* 18:105-110 in view of Cox *et al.*, 1995, *Am. J. Obstet. Gynecol.* 172:946-54. With respect to Nuovo *et al.*, the Action states that this reference discloses a reagent for detecting human papilloma virus DNA in a cell sample comprising a plurality of genomic DNA probe sets, wherein each probe set comprises a plurality of nucleic acid fragments of essentially the entire full-length genomic sequence of HPV types 16 and 18, as well as a similar reagent that hybridizes to HPV types 31, 33, and 35. The Action also states that Nuovo *et al.* disclose probe mixes provided by Digene Diagnostics that are made using the entire genome and that contain probes for these groups of HPV subtypes. The Action further states that the probes in the kits provided by Digene Diagnostics would have inherently been in containers. The Action, however, acknowledges that Nuovo *et al.* does ***not*** disclose a reagent comprising genomic probe sets derived from all of the HPV types listed in claim

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1.

With respect to Cox *et al.*, the Action states that this reference discloses a single reagent comprising RNA probes to a group of high-risk HPV types including types 16, 18, 31, 33, 35, 45, 51, 52, and 56, and suggests expanding the assay to include probes to HPV types 39 and 58. The Action asserts that it would have been *prima facie* obvious at the time the invention was made to modify the reagents disclosed by Nuovo *et al.* so as to provide a single reagent including nick-translated DNA probes to all of the HPV types disclosed by Cox *et al.* The Action also asserts that one of ordinary skill in the art would have been motivated to make a DNA probe cocktail capable of detecting the same high-risk HPV types as the RNA probe cocktail disclosed by Cox *et al.* because DNA probes are more stable in solution than RNA probes.

The Action states that the probes taught by Nuovo *et al.* in view of Cox *et al.* would satisfy the requirement that "the nucleic acid fragments of the genomic HPV DNA probe sets do not detectably hybridize to the genomic sequence of a low-risk HPV type," since at very high stringency conditions, cross-hybridization with low-risk HPV types would not be expected. The Action also states that the cross-hybridization of the probes taught by Nuovo *et al.* in view of Cox *et al.* to the genomic sequences of HPV types 39, 45, 52, 56, 58, 59, 68, and 70 is a necessary property of the probe set, as evidenced by the instant specification which teaches that a full-length nick-translated genomic probe to HPV type 18 hybridizes to HPV types 18, 39, 45, 56, 59, 68, and 70, and a full-length nick-translated genomic probe to HPV type 33 hybridizes to HPV types 16, 31, 33, 35, 45, 52, and 58.

Applicants note that an analysis of obviousness must be based on the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviosuness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Moreover, where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 *also requires* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). As the Federal

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Circuit has emphasized: "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not the Applicants' disclosure." *Id.*

Applicants contend that the accompanying Declaration Pursuant to 37 C.F.R. § 1.132 of Gerard J. Nuovo sets forth affirmative evidence establishing that Nuovo *et al.* in view of Cox *et al.* does not result in a *prima facie* case of obviousness with respect to claims 1, 3, and 17. In particular, while Nuovo *et al.* disclose the use of four high-risk HPV consensus probes obtained from Digene Diagnostics and ONCOR that contain probes generated from specific subgenomic areas of (i) HPV types 16 and 18 or (ii) HPV types 31, 33, and 35 (Declaration, para. 8), this reference does not disclose the specific proportions of the probes in the Digene Diagnostics or ONCOR high-risk HPV consensus probes (*id.* at para. 9). Moreover, because the Cox *et al.* reference does not suggest – and, in fact, persons of ordinary skill in the art other than the inventors did not appreciate at the time the instant application was filed – that unexpected results (*i.e.*, preparing a high-risk HPV consensus probe that cross-hybridizes with other high-risk HPV types under low stringency conditions, but does not detectably hybridize to the genomic sequence of a low-risk HPV type) could be obtained by decreasing the proportions of certain probes in the high-risk HPV consensus probe (*id.*, para. 11), the deficiencies and limited disclosure of Nuovo *et al.* cannot be cured by combining the teachings of this reference with those of the Cox *et al.* reference. In other words, even if Nuovo *et al.* in view of Cox *et al.* were to suggest a reagent comprising a plurality of genomic HPV DNA probe sets that comprise a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequences of HPV types 16, 18, 31, 33, 35, and 51 (a point that Applicants do not concede), these references clearly do not suggest that the proportions of total HPV DNA in the reagent comprising nucleic acid fragments of HPV type 16 and 31 DNA should be decreased relative to the proportions of the total HPV DNA in the reagent comprising HPV type 18, 33, 35, and 51. Thus, absent Applicants' teachings, one ordinary skill in the art would simply not be motivated to make the reagent of claim 1.

In addition, Applicants maintain that one of ordinary skill in the art would not think to substitute the RNA probes of the hybrid capture method disclosed by Cox *et al.* with genomic DNA probes because genomic probes would simply not work in the hybrid capture method disclosed by Cox *et al.* In the hybrid capture method disclosed by Cox *et al.*, single-stranded DNA isolated from

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a cell sample is allowed to hybridize to RNA probes corresponding to a number of high-risk HPV types, and RNA/DNA hybrids that form are immobilized in a capture tube coated with antibodies specific for RNA/DNA hybrids (p. 948). Since the use of a reagent comprising RNA probes is a ***necessary*** requirement of the method disclosed by Cox *et al.*, a skilled artisan practicing the method of Cox *et al.* would not think to substitute the RNA probes of that method with genomic DNA probes.

Moreover, because of the substantial differences between the hybrid capture method disclosed by Cox *et al.* and the assay disclosed in the instant application, one of ordinary skill in the art would not have looked to Cox *et al.* for teachings that might be relevant to the assay disclosed in the instant application. For example, at the time the Cox *et al.*, 1995 reference was published, a person of ordinary skill in the art would have appreciated that a hybrid capture probe reagent such as the one disclosed by Cox *et al.* ***would*** detectably hybridize to the genomic sequence of a low-risk HPV type – as well as generate false positives with respect to low-risk HPV types (*id.*, para. 13). In fact, at the time the above-described application was filed, a person of ordinary skill in the art would have expected a high-risk HPV consensus probe to detectably hybridize to the genomic sequence of both low-risk and high-risk HPV types under low stringency conditions, and to not detectably hybridize to the genomic sequence of either low-risk HPV types or high-risk HPV types other than those used to generate the high-risk HPV consensus probe under high stringency conditions (*id.*, para. 14). Clearly, then, Applicants' disclosure in the instant application of a high-risk HPV consensus probe that cross-hybridizes under low stringency conditions with high-risk HPV types other than those used to generate the high-risk HPV consensus probe, while not detectably hybridizing to the genomic sequence of low-risk HPV types, is surprising and unexpected.

Thus, even if one of ordinary skill in the art would not have thought to mix the high-risk HPV consensus probes disclosed by Nuovo *et al.* (*i.e.*, the high-risk HPV consensus probes generated from specific subgenomic areas of HPV types 16/18 and HPV types 31/33/35), absent Applicants' teachings, a skilled artisan would not have been able to determine the proportions of the HPV type-specific probes required to generate a cross-hybridizing high-risk HPV consensus probe that does not detectably hybridize to the genomic sequence of a low-risk HPV type under low stringency conditions. In addition, one of ordinary skill in the art would not have considered preparing DNA - rather than RNA - capture probes, since the former would simply not function in

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hybrid capture protocol. There can be no simpler demonstration of this fact than Digene Diagnostics' and ONCOR's manufacture and sale of two ***separate*** HPV cocktails. Finally, one of ordinary skill in the art would not have thought to recreate the RNA probe cocktail of Cox *et al.* using genomic DNA probes because, absent Applicants' teachings, the skilled artisan would not understand that a reagent comprising genomic HPV DNA probe sets would allow for the detection of high-risk HPV types ***without*** cross-reacting with low-risk HPV types. Applicants contend that for the reasons listed above, Nuovo *et al.* in view of Cox *et al.* does not result in a *prima facie* case of obviousness with respect to claims 1, 3, and 17. Withdrawal of this rejection is therefore respectfully solicited.

b. Rejection of claims 7 and 22 as being unpatentable over Nuovo *et al.* in view of Cox *et al.*, and further in view of Bauer *et al.*

The Office Action mailed May 18, 2006 asserts a rejection of claims 7 and 22 under 35 U.S.C. § 103(a), as being unpatentable over Nuovo *et al.*, 1995, *J. Histotechnology* 18:105-110 in view of Cox *et al.*, 1995, *Am. J. Obstet. Gynecol.* 172:946-54, and further in view of U.S. Patent No. 5,639,871 (Bauer *et al.*). The Action's assertions with respect to Nuovo *et al.* and Cox *et al.* are set forth above in section 2(a). The Action states that Nuovo *et al.* in view of Cox *et al.* do not disclose a reagent comprising probes that are present in the proportions recited in claim 7, but that the optimization of hybridization assays by determining ideal probe concentrations was routine in the prior art at the time the invention was made (as exemplified by Bauer *et al.*). The Action asserts that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have experimented with different probe concentrations so as to arrive at an optimal concentration for the detection of HPV in a sample.

As discussed above, Nuovo *et al.* in view of Cox *et al.* does not result in a *prima facie* case of obviousness with respect to claims 1, 3, and 17. Because Bauer *et al.* does not disclose – and, in fact, persons of ordinary skill in the art other than the inventors did not appreciate at the time the instant application was filed – that a high-risk HPV consensus probe that does not detectably hybridize to the genomic sequence of a low-risk HPV type under low stringency conditions could be prepared by decreasing the proportions of certain probes in the high-risk HPV consensus probe (*id.*, para. 11), the deficiencies and limited disclosure of Nuovo *et al.* in view of Cox *et al.* cannot be

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cured by combining the teachings of these references with those of Bauer *et al.* In other words, absent Applicants' teachings, a skilled artisan would have had no reason to decrease the proportions of only two of the six probes in the high-risk HPV consensus probe allegedly disclosed by Nuovo *et al.* in view of Cox *et al.* Thus, decreasing the proportions of total HPV DNA in the reagent comprising nucleic acid fragments of HPV type 16 and 31 DNA relative to the proportions of the total HPV DNA in the reagent comprising HPV type 18, 33, 35, and 51 constitutes undue experimentation and not mere optimization. For such experimentation to constitute optimization, a form of the high-risk HPV consensus probe allegedly disclosed by Nuovo *et al.* in view of Cox *et al.* that has not been optimized (*i.e.*, one containing standard amounts of each HPV type-specific probe) must ***not*** detectably hybridize to the genomic sequence of a low-risk HPV type under low stringency conditions. However, as described in the accompanying Declaration, a high-risk HPV consensus probe comprising a standard amount of HPV type 16 DNA ***would*** detectably hybridize to HPV types 6/11 under low stringency conditions (Declaration, para. 5). Applicants also note that because the high-risk HPV consensus probe allegedly disclosed by Nuovo *et al.* in view of Cox *et al.* would not detectably hybridize to the genomic sequence of a low-risk HPV type under high stringency conditions, there would be no reason to decrease the proportion of any individual probe for use under high stringency conditions. Because undue experimentation – and not mere optimization – would be required to prepare the high-risk HPV consensus probe allegedly disclosed by Nuovo *et al.* in view of Cox *et al.*, Applicants contend that Nuovo *et al.* in view of Cox *et al.*, and further in view of Bauer *et al.*, does not result in a *prima facie* case of obviousness with respect to amended claim 1. Withdrawal of this rejection is therefore respectfully solicited.

3. Provisional rejection of claims 1, 3, 7, 17, 19, and 22 for obviousness-type double patenting

The Action asserts a provisional rejection of claims 1, 3, 7, 17, 19, and 22 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 17-22 of U.S. Application No. 10/646,633.

Applicants acknowledge the rejections under the doctrine of obviousness-type double patenting, and elect to address these grounds of rejection by submitting a Terminal Disclaimer or by argument upon notification that all other conditions for patentability have been met, and the claims

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are otherwise in condition for allowance.

CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner Switzer believes it to be helpful, she is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
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Dated: November 20, 2006

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